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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,977	10/02/2003	Jack Nguyen	33328.04905.US01/4905	9061

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,977	NGUYEN ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,3-7,9,11-16,45,48,51-53,57-59,61-63 and 65-78* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3-7,9,11-16,45,48,51-53,57-59,61-63 and 65-78* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/23/11, 1/9/12*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3-7, 9, 11-16, 45, 48, 51-53, 57-59, 61-63 and 65-78 are pending and under examination in the application.

Withdrawn Rejection

Any rejections in the previous office action that are not repeated below have been withdrawn.

New Rejections-Necessitated by Amendments

Claim Rejections - 35 USC § 112

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 53, 59 and 63 step (e) which recites "to verify that the function of the target protein has been inactivated by the cleavage event..", "the protease mutein or biologically active portion thereof cleaves a substrate sequence in the

target protein that is different from a native substrate sequence of the wild-type mammalian protease scaffold" and step c) of "the polypeptide comprising the substrate sequence that is present in the target protein" are not supported in the as-filed specification. MPEP 2163.06 clearly states that applicants point out support in the specification for the new claim limitations.

Claim Rejections - 35 USC § 112

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 1 is vague and indefinite as to the treatment of disease with the inactivation of the activity of the target. The preceding claim recites only involvement (not cause) of the target in the disease. The metes and bounds of said treated disease are not clear for treatment by any kind or all kinds of mutated scaffold of protease.

2. Claims 1, 53, 59 and 63 recite the limitation "the function" of the target protein. There is insufficient

antecedent basis for this limitation in the claim and vague as to which function is being referred to.

3. Claims 3 and 4 recite the limitation "the number of mutations". There is insufficient antecedent basis for this limitation in the claim and vague as to the number being referred to.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Lien et al(Combinatorial Chemistry and High Throughput Screening, 1999(in view of either Harris et al (The Journal of Biological Chemistry)(I) or (Current Opinion in Chemical Biology(II)(as evidenced by Shi et al, (USP 20020197701) and Waugh et al (Nature Structure Biology) for reasons of record as reiterated below and modified to address the claim amendments.

For claims 1, 3-7, 13, 16, 45, 51-53, 57-59, 61 and 67-78, Lien discloses at e.g., pages 73-75 a method of identifying serine proteases using targeted combinatorial mutagenesis of serine proteases with N mutations (e.g., Fig. 1, page 74). The method comprises producing sizeable libraries of mutant enzymes (N mutations), contacting the library with a substrate and identifying the mutant. Screening and selecting methods both depend not only on the activity and specificity of mutant proteins but also on their individual expression levels (e.g., page 77, col. 1, first complete paragraph). Lien discloses at e.g., page 77, first incomplete paragraph, and quantitative assessments of cleavage made by monitoring the hydrolysis of a set of synthetic peptides esters in a colorimetric plate assay (testing as claim). Lien discloses at e.g., page 73 that the mutant enzyme is useful for therapy as in blood coagulation.

Lien discloses at e.g., pages 77-80 mutations of amino acids at positions 215 and 216. Lien discloses that positions 191 and 192 are tolerant to substitutions where small residues are preferred for position 191, his for 213; M190A. Fig. 2 shows the residues targeted for amino acid substitutions such as, 190, 191, 192 and 218 (recited as among the between residues in claim 1).

For claim 13, Lien discloses mutants with improved cleavage of at least 62.

For Claim 56, Lien discloses that phage displayed proteins can be subjected to in vitro selection procedures, e.g., page 77, first incomplete paragraph, col. 1.

For claims 16, 45, 57, Lien discloses at e.g., page 74, chemical mutagenesis, passage through bacterial mutator strains and PCR. (See also e.g., paragraph bridging pages 76-77.)

For claim 52 Lien discloses at e.g., page 76, col. 2 "in vivo" selection.

For claim 61, Lien discloses at e.g., page 86, col. 2, first incomplete paragraph, granzyme B.

For claims 69, 72, 75 and 78, Lien et al discloses at e.g., page 76, col. 2, and last incomplete paragraph chromogenic substrates.

For claims 68, 71, 74 and 77 Lien discloses at e.g., page 78, cols. 1-2, under Screening Methods, tetrapeptide with P1=Phe.

The claim inactivation of a target protein involved with a disease or pathology in a mammal that treats a disease is a property implicit, if not inherent, to the method of Lien et al which teaches similar process steps and compound in the method. Lien teaches at e.g., page 73, col. 1:

> "…{i}t is useful to be able to generate proteases with new and desirable **cleavage specificities**. Such enzymes….. could have practical applications in biotechnology…. therapy (modulation of zymogen cascades, such as blood coagulation)….

[This is evident from the teachings of Shi et al at e.g., paragraph [0003])

Shi teaches at e.g., paragraph [003]:

> Members of the serine protease family which play important roles in a range of cellular functions and which have demonstrated causative roles in human diseases include tissue- type plasminogen activator and thrombin (thrombosis and blood clotting), urokinase-type plasminogen activator (cancer and metastasis), trypsin and elastase (emphysema and liver disease) and angiotensin converting enzyme (hypertension).

Lien does not disclose the enzyme as granzyme (albeit suggests said granzyme, above) and the substrate as caspase (elected species).

Harris et al discloses at e.g., page 27364, identification of in vivo targets of granzyme B based on the elucidation of the substrate specificity of granzyme B. For example, Harris et al. teaches that based on the substrate specificity of granzyme B, certain caspases (caspases 3 and 7), based on their sequences, are more likely substrates then other caspases. Harris et al., also teaches that based on the sequence specificity of granzyme B, nuclear lamin A and nuclear poly(ADP)ribose polymerase (PARP)

are potential in vivo substrates for granzyme B. Harris et al. I also teaches that amino acid position Arginine 192 is a structural determinant of specificity of granzyme B, since granzyme B mutations R192E and R192A exhibit reduced hydrolysis of the optimal tetrapeptide substrate Ac-IEPD-AMC and non-optimal tetrapeptide substrate Ac-IKPD-AMC compared to the wild-type enzyme. Harris also discloses at e.g., pages 27372 up to and 27373:

> ….{T]here is a functional relationship between the preferential substrate sequence of granzyme B and the activation site of members of the caspases (Fig. 5D). Indeed, studies have shown that granzyme B cleaves and activates several **caspases involved in apoptosis.** Our data on the substrate specificity of granzyme B suggest that caspase 3 and caspase 7 are preferentially activated during apoptosis. Knowledge of the extended substrate specificity of granzyme B allows for the proposal of additional targets of granzyme B during apoptosis. The substrate specificity of caspase 6 matches that of granzyme B, suggesting that both enzymes cleave the same substrates. Several proteins known to be cleaved during apoptosis, such as nuclear lamin A….
> The identification of their specificity will further expand our knowledge of the role that granzymes play in **cytotoxic, lymphocyte-mediated cell death.**

Harris (II) throughout the article, at e.g., pages 127-129, basically discloses the same method as Harris (I).

Waugh discloses at page 762 that granzymes are a vital component of the cytotoxic lymphocyte’s ability to induce apoptosis, contributing to rapid cell death of a tumor or

virally infected target cell by the cleavage of downstream substrates and the activating cleavage of caspases.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use as the serine protease granzyme in the method of Lien. Harris teaches that granzyme is a substrate for caspases or caspases can act as substrate depending on its sequence. Accordingly, one would have a reasonable expectation of success in using other serine protease, such as granzyme as taught by Lien as the other serine proteases. Furthermore, one would have a reasonable expectation of success in using granzyme as an enzyme for caspase substrate depending upon the sequence contain in each enzyme as taught by Harris above. One would be motivated to use either caspase or granzyme to act as enzyme or substrate due to the dual role each enzymes exhibits depending upon the sequence that is contained therein. Furthermore, caspase and granzyme are only the two most specific of proteases, with an unusual and absolute requirement for cleavage after aspartic acid.

Response to Arguments

Please note that the responses in the previous office actions are similarly incorporated herein in view of applicants' incorporation of their arguments from the previous actions.

Applicants argue that Lien et al does not teach or suggest a method that includes claim steps d) and e) including the claim cleavage of the substrate sequence inactivates an activity of the target protein.

In reply, attention is drawn Lien at e.g., page 83, col. 2 which recites that the "findings were validated when direct measurement of kcat/km values for peptide that had been synthesized and cleaved individually". The claim steps would have been obvious given that Lien teaches identification of said protease muteins using known techniques of testing.

Applicants further argue that Harris I teach two mutants of granzyme B at amino acid residue 192 in granzyme B that reduces its hydrolysis of an optimal tetrapeptide substrate and not increased cleavage activity and/or substrate specificity for a target protein.

Harris et al. I teach at page 27364, 2nd column:

> Although granzyme B is the only known mammalian serine protease to have Pl-proteolytic specificity, it is shared with the caspases, a family of cysteine proteases that are also activated during apoptosis. The link between granzyme B and the caspases has been strengthened by studies indicating that **granzyme B can cleave and activate certain members of the caspases**, and it has been suggested that this is one of the mechanisms by which granzyme B mediates apoptosis in vivo. [Emphasis added]

Harris et al., thus, teaches that cleavage by granzyme activates its target protein.

In reply, as correctly stated by applicants, Harris teaches "certain members of the caspases" and not all. While the claims recite the argued function however, because the broad claim does not recite any amino acids that would replace the claim residues at the claim positions hence, it is very likely that not all mutations would result in cleavage of the substrate sequence that inactivates an activity of the target protein.

For example, Harris teaches mutations of 192 to glutamate activate caspase 7(see the abstract) which is different from the caspase-3 disclosed in the specification that is inactivated by the single mutant granzymeB I99A/N218A. (The claims recite for several mutants). Since there are apparently several caspases, activation and inactivation appear to be sequence dependent, as taught by the reference above. See also the teachings of Lien, in its entirety.

Furthermore, Harris and Waugh are not employed for the purpose as argued. Rather for its teachings of the specific protease, granzyme and substrate, caspase since the claim steps are taught by Lien.

The combined teachings of the prior art renders the claim prima facie obvious to one having ordinary skill in the art at the time the invention was made. The claimed method steps are

routine steps in the art of screening and identifying a **specific** mutant from a library of mutants that binds to a **specific** target protein. The claim method is nothing more than a predictable result expected of the method of screening protease muteins against a target protein. KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

Double Patenting

Claims 1-7, 9, 11-16, 45, 48, 51-53, 56-59, 61-63 and 65-78, as amended, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, for example, of copending Application No. 12/005949 ('949 application). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claim method is similar, if not nearly identical to the method of the '949 application. The subject matter of the instant and the '949 applications overlap in scope.

Response to Arguments

Applicant requests deferral of resolution of this issue. It is premature to file a terminal disclaimer at this time. If, when one or both applications are deemed allowed, it is

determined that a terminal disclaimer is necessary, Applicant will file a terminal disclaimer.

In reply, in the absence of a terminal disclaimer, the rejection is maintained.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner

Art Unit 1636